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THERAPY IN PRACTICE

A Practical Guide to the Treatment of Dravet Syndrome with Anti-Seizure Medication

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Abstract

Dravet syndrome is a severe developmental and epileptic encephalopathy characterised by refractory seizures and cognitive dysfunction. The treatment is challenging, not least because the seizures are highly drug resistant, requiring multiple anti-seizure medications (ASMs), while some ASMs can exacerbate seizures. Initial treatments include the broad-spectrum ASMs valproate (VPA), and clobazam (CLB) in some regions; however, they are generally insufficient to control seizures. With this in mind, three adjunct ASMs have been approved specifically for the treatment of seizures in patients with Dravet syndrome: stiripentol (STP) in 2007 in the European Union and 2018 in the USA, cannabidiol (CBD) in 2018/2019 (in combination with CLB in the European Union) and fenfluramine (FFA) in 2020. These "add-on" therapies (mostly to VPA/CLB) are used as escalation therapies, with the choice dependent on availability in different countries, patient characteristics and caregiver preferences. Topiramate is also frequently used, with evidence of efficacy in Dravet syndrome, and there is anecdotal evidence of efficacy with bromide, which is frequently used in Germany and Japan. With a growing treatment landscape for Dravet syndrome, there can be practical challenges for clinicians, particularly with issues associated with polypharmacy. This practical guide provides an overview of these main ASMs including their indications/contraindications, mechanism of action, efficacy, safety and tolerability profile, dosage requirements, and laboratory and clinical parameters to be evaluated. Standard laboratory and clinical parameters include blood counts, liver function tests, serum concentrations of ASMs, monitoring the growth of children, as well as weight loss and acceleration of behavioural problems. Regular cardiac monitoring is also important with FFA as it has previously been associated with cases of cardiac valve disease when used in adults at high doses (up to 120 mg/day) in combination with phentermine as a therapy for obesity. Importantly, no signs of heart valve disease have been documented to date at the low doses used in patients with developmental and epileptic encephalopathies. In addition, potential drug–drug interactions and their consequences are a key consideration in everyday practice. Interactions that potentially require dosage adjustments to alleviate adverse events include the following: STP + CLB resulting in increased plasma concentrations of CLB and its active metabolite norclobazam may increase somnolence, and an interaction with STP and VPA may increase gastrointestinal adverse events. Cannabidiol has a bi-directional interaction with CLB producing an increase in plasma concentrations of 7-OH-CBD and norclobazam resulting in the potential for increased somnolence and sedation. In addition, CBD is associated with elevations of liver transaminases particularly in patients taking concomitant VPA. The interaction between FFA and STP requires a dose reduction of FFA. Furthermore,

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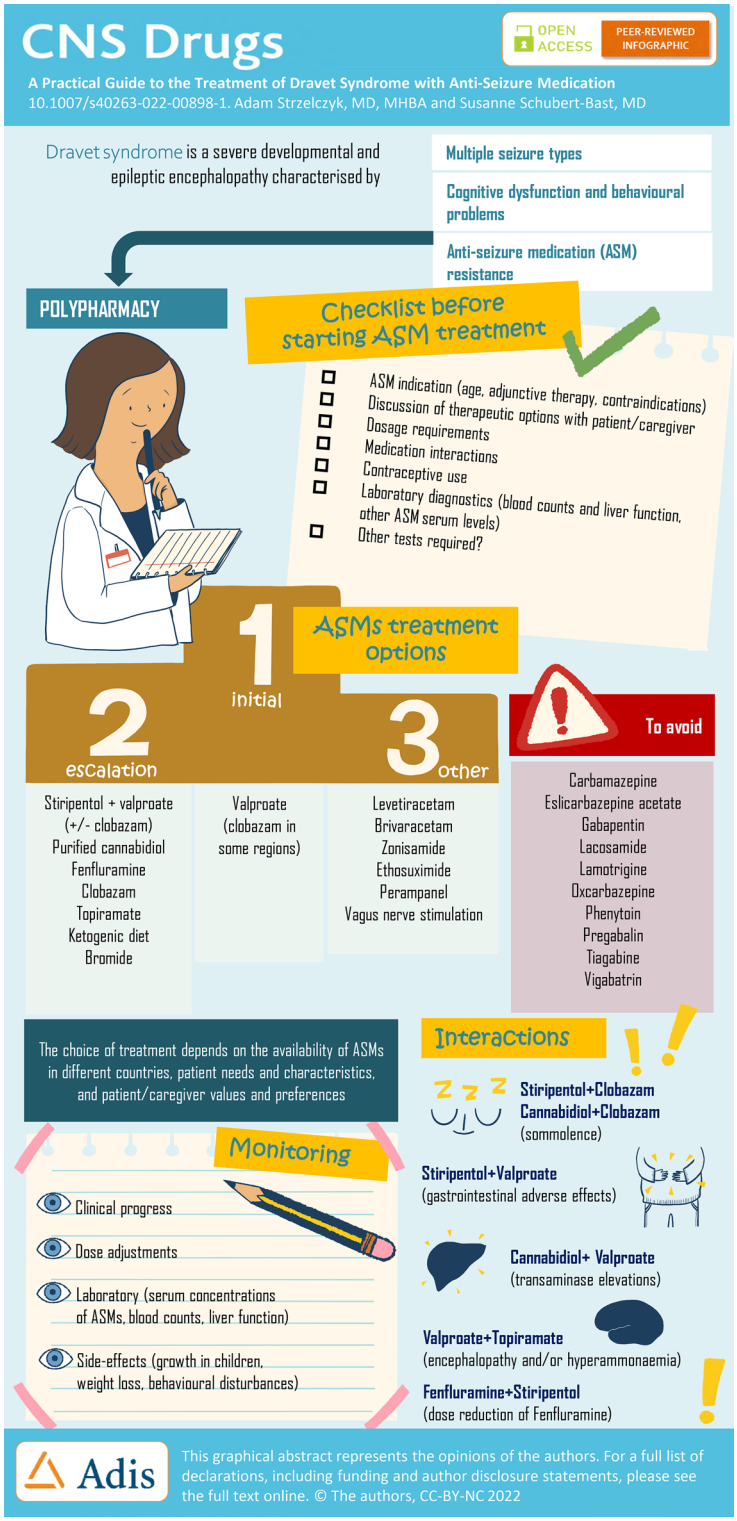
concomitant administration of VPA with topiramate has been associated with encephalopathy and/or hyperammonaemia. Finally, we briefly describe other ASMs used in Dravet syndrome, and current key clinical trials.

Graphical abstract



Key Points

Patients with Dravet syndrome are treated with multiple anti-seizure medications to control seizures including valproate (VPA), and clobazam (CLB in some regions), as initial therapy, and stiripentol (STP), cannabidiol (CBD) or fenfluramine (FFA) as escalation therapies; alternatives include topiramate (TPM), bromide, levetiracetam, brivaracetam, zonisamide, ethosuximide and perampanel.

Because polypharmacy is the norm in Dravet syndrome, there are practical pitfalls that include changes in serum concentrations of anti-seizure medications and the potential for increased adverse events, requiring careful monitoring and possible dose adjustments.

Key interactions that may require dosage adjustments to alleviate adverse events include STP+CLB (somnolence), STP+VPA (gastrointestinal adverse events), CBD+CLB (somnolence), CBD+VPA (liver transaminase elevations), FFA+STP (dose reduction of FFA) and VPA+TPM (encephalopathy and/or hyperammonaemia).

1 Introduction

Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterised by drug-resistant seizures and cognitive dysfunction, negatively impacting on the quality of life of the patients and their families [1, 2]. In the majority of cases, it is caused by heterozygous loss-of-function variants in the *SCN1A* gene, resulting in substantially decreased levels of the corresponding functional protein, the α-1 subunit of the neuronal, voltage-gated sodium channel $Na_V1.1$ [3]. $Na_V1.1$ is a key sodium channel in the central nervous system that is highly expressed in many GABAergic inhibitory neurons, and the impairment of the production of this protein leads to hyperexcitability of the neuronal network [4].

As with other developmental and epileptic encephalopathies, the management of DS is challenging (Fig. 1). First, DS is associated with multiple seizure types that evolve over time [2, 3, 5]. Seizures typically begin before the age of 1 year, in a formerly healthy infant, usually with tonic-clonic or clonic febrile seizures. Between the ages of 1 and 5 years, afebrile seizure types emerge including generalised motor, atypical, myoclonic and absence. Seizures are often prolonged, and status epilepticus (SE) is common especially in the patient's first 5 years. Beyond the age of 5 years, seizure frequency begins to decrease, with a gradual transition with age to nocturnal seizures, which are the main type of seizures in adults. Nocturnal seizures can also pose challenges including sleep disturbances for both patients and their family members [6]. Nocturnal seizures, SE and sudden unexpected death in epilepsy result in a higher mortality rate compared with patients with other epilepsy [7]. In addition to seizures, patients experience varying degrees of cognitive dysfunction and behavioural problems. As such, even though the seizure burden may dissipate with age, there remains a high level of dependency throughout the patient's life [6].

Another challenge is that some anti-seizure medications (ASMs) can exacerbate seizures in DS (Fig. 2), and therefore an early diagnosis is important to make sure patients are treated appropriately (Fig. 1). In addition, high seizure frequency is associated with a lower quality of life, and may be correlated with cognitive dysfunction, further highlighting the importance of a prompt diagnosis and timely treatment of seizures [8–12].

Patients are usually treated with multiple ASMs in an attempt to control seizures, with valproate (VPA) and clobazam (CLB) generally being inadequate (**Fig. 2**) [13–15]. With this in mind, three ASMs specifically approved as adjunct therapies in patients with DS have become available in the last decade: stiripentol (STP), which was approved in 2007 in the European Union (EU) and 2018 in the USA, cannabidiol (CBD) approved in 2018/2019 and fenfluramine (FFA) approved in 2020 (Fig. 2) [13, 14, 16, 17]. These treatments are "add-on" therapies (most commonly to VPA and CLB), with the choice dependent on availability and recommendations in different countries, among other factors (Fig. 2) [13, 14, 16, 17]. Overall, an individualised approach to treatment should be employed, taking into account patient needs, together with patient/caregiver values and preferences to collaboratively choose the most appropriate treatment [18, 19].

With a growing treatment landscape for DS, the complexity surrounding treatment decisions increases, causing practical challenges for clinicians (Fig. 1). Herein, we provide a practical guide to the main ASMs that have evidence of efficacy in the treatment of seizures in DS. We provide an overview of the indications and contraindications, their mechanism of action, efficacy, safety and tolerability profile, dosage requirements, and laboratory and clinical parameters to be evaluated. In addition, because of the need for polypharmacy, potential drug–drug interactions (in particular with other relevant ASMs and with hormonal contraceptives) and their consequences are described. Figure 3 provides a checklist of these considerations, with signposts to the relevant tables that provide further details, in addition to the narrative below. The focus of this guide is on the pharmacological treatment of seizures with ASMs, although it should be noted that patients with DS may also use other medications

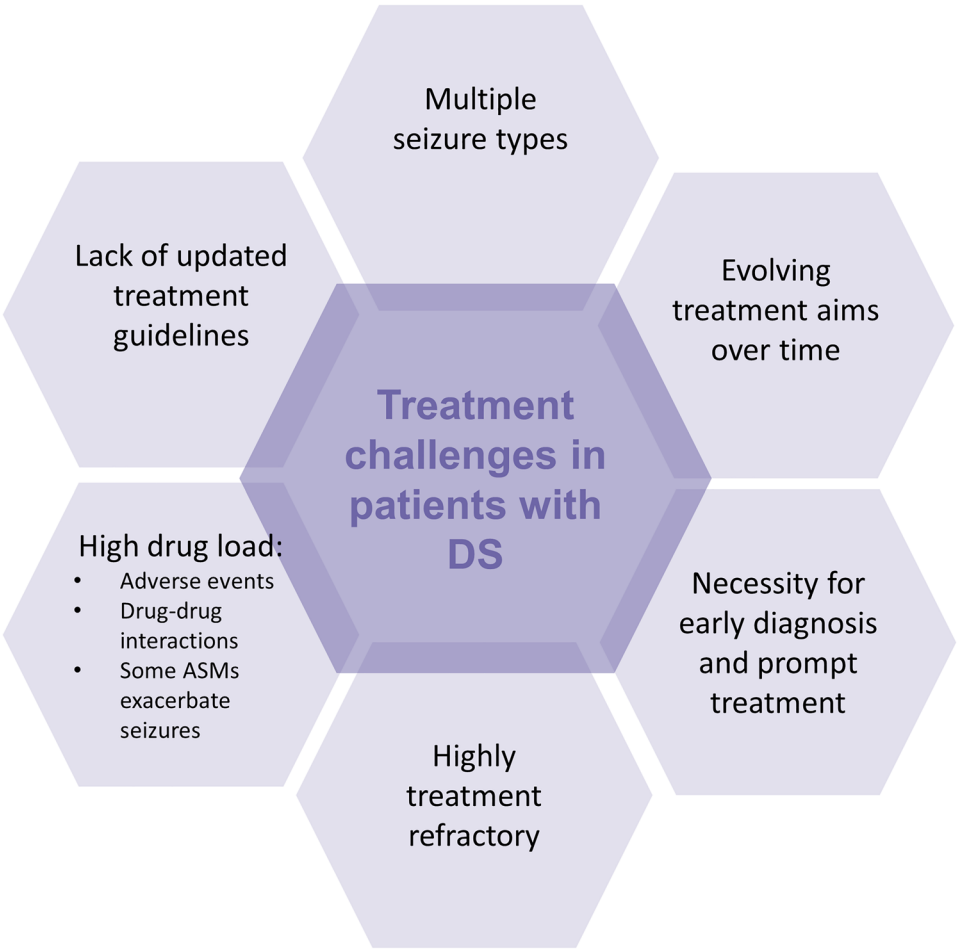


Fig. 1 Treatment challenges in patients with Dravet syndrome (DS). *ASMs* anti-seizure medications

for behavioural and sleep problems, as well as emergency rescue medication [20, 21]. In addition, non-pharmacological interventions, including the ketogenic diet and vagus nerve stimulation in carefully selected patients, can also help alleviate seizures but are not covered in this guide.

2 Valproate (VPA)

Valproate, a widely used agent for epilepsy in all ages, is the first-line treatment for patients with DS (Fig. 2). Valproate is a broad-spectrum ASM effective across a range of focal and generalised seizure types including tonic-clonic, myoclonic, tonic and absence seizures (see Table 1 for the indications in the EU/UK and the USA). The wide-ranging activity is likely a reflection of its complex mechanism of action modulating various targets implicated in the development of seizures, including the inhibitory neurotransmitter GABA, voltage-gated sodium channels and histone deacetylase (Fig. 4) [22]. Valproate has proved effective in generalised and unclassifiable epilepsies [23, 24], and is generally well tolerated, an important contributing factor behind its extensive use in epilepsy.

Valproate is available in a variety of formulations including tablets (regular, crushable, gastro-resistant and prolonged release) and granules (modified release), oral solution (liquid and syrup), as well as a solution for injection or infusion. The starting dose of VPA is typically between 10 and 15 mg/kg/day, divided into two doses for the generally favoured prolonged-release formulation or three doses otherwise, followed by gradual increases to target doses in the range of 25 to a maximum of 60 mg/kg/day according to clinical response and tolerability. In cases where acceptable clinical response has not been attained, plasma concentrations of VPA should be checked to see if they are in the generally accepted therapeutic range of 50–100 mcg/mL. Of note, VPA is also being trialled in patients with drug-resistant epilepsy for long-term intra-cerebroventricular drug delivery, a novel method using an implantable infusion system that administers the drug into the cerebrospinal fluid [25].

Valproate has a generally acceptable safety profile. The most common adverse events (AEs) include gastrointestinal

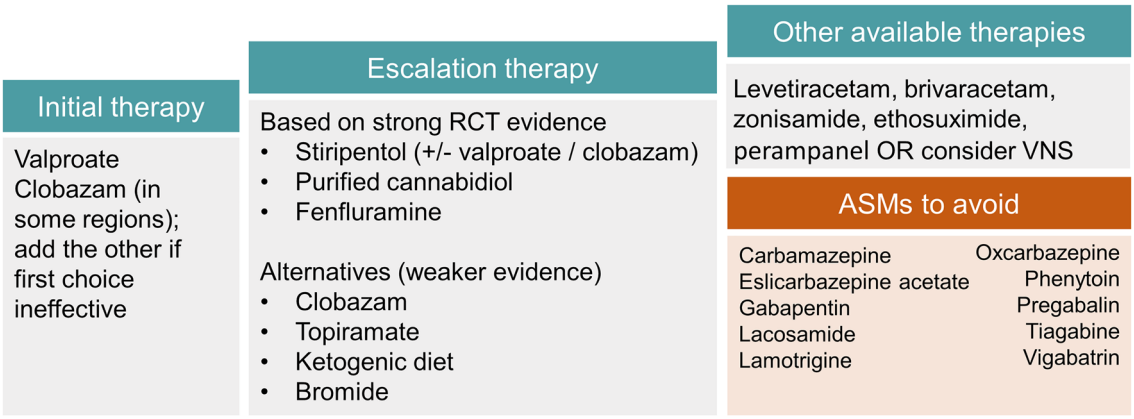


Fig. 2 Treatment pathway in patients with Dravet syndrome. Adapted from Cross et al. [124]. The choice of treatment is dependent on the drug availability and recommendations in different countries, patient needs and characteristics, and patient/caregiver values and preferences. *ASMs* anti-seizure medications, *RCT* randomised controlled trial, *VNS* vagus nerve stimulation

disturbances (nausea, vomiting and abdominal pain and diarrhoea), headache, somnolence, tremor and asthenia, although these are generally mild to moderate in severity and reduce over time [26, 27]. However, VPA has been associated, albeit rarely, with serious and fatal hepatotoxicity, with children < 2 years of age (especially those taking multiple ASMs) and people with mitochondrial disorders caused by mutations of the mitochondrial *DNA Polymerase γ* (*POLG*) gene at particular risk [26, 27]. As such, VPA is contraindicated in patients with hepatic disease or significant hepatic dysfunction and those with hereditary *POLG1*-associated mitochondrial disease; of note, rare cases of *POLG1* mutations in patients with DS have been reported [28, 29]. Before initiating VPA, liver function tests are required to exclude liver disease and patients should be monitored regularly thereafter, particularly during the first 6 months [26, 27]. A physical examination and a medical history should also be conducted as liver function tests are not always abnormal, and instead, non-specific symptoms including malaise, weakness, lethargy, facial oedema, anorexia and vomiting, as well as a loss of seizure control, have been reported to occur prior to cases of serious/fatal hepatotoxicity [26, 27]. Valproate is also associated with coagulation disorders (including thrombocytopenia, decreases in von Willebrand's factor and platelet dysfunction) and hyperammonaemia. Therefore, in addition to liver enzymes, laboratory tests should include blood count and ammonia; tests should be performed before treatment initiation and then repeated after 6 weeks, 3 months and 6 months after treatment initiation, and then in yearly intervals (Table 2). In addition, coagulation parameters, platelet count and platelet function should be tested if surgery is planned.

There is a paucity of studies evaluating VPA as monotherapy in patients with DS, with three retrospective studies reporting >50% responder rates of 23–52% [30–32]. However, VPA alone is generally insufficient to control seizures in DS and persisting seizures leads to further add-on treatments. Therefore, as polypharmacy is the norm in DS, an awareness of the consequences of potential drug–drug interactions and the potential for AEs with other ASMs is a key consideration (Table 3). Of note, concomitant administration with topiramate (TPM) has been associated with encephalopathy and/or hyperammonaemia; the signs and symptoms should be carefully monitored especially in patients with pre-existing encephalopathy (Table 3) [26, 27]. Valproate is an inhibitor of a broad range of hepatic enzymes (cytochrome P450s, uridine glucuronyl transferases and epoxide hydrolase, among others) that are involved in the metabolism of other ASMs, resulting in increased serum concentrations of these substrates including lamotrigine, phenobarbital, the metabolite 10,11-epoxide of carbamazepine, ethosuximide and rufinamide. While these ASMs are rarely used in DS, it may still be worth noting that increased monitoring of ASM concentrations and dosage adjustments are required when these drugs are initiated or withdrawn. In particular, an increased risk of serious skin conditions (Stevens–Johnson syndrome and toxic epidermal necrolysis) has been reported with concomitant lamotrigine, requiring a slow titration of lamotrigine at initiation. Furthermore, the use of oestrogen-containing contraceptives can lead to decreased efficacy of VPA requiring monitoring (Table S1 of the Electronic Supplementary Material [ESM]).

3 Clobazam (CLB)

As with VPA, CLB is widely used for the treatment of developmental and epileptic encephalopathies including DS, owing to its favourable tolerability, safety and broad-spectrum anti-seizure activity. In the EU, CLB has a broad

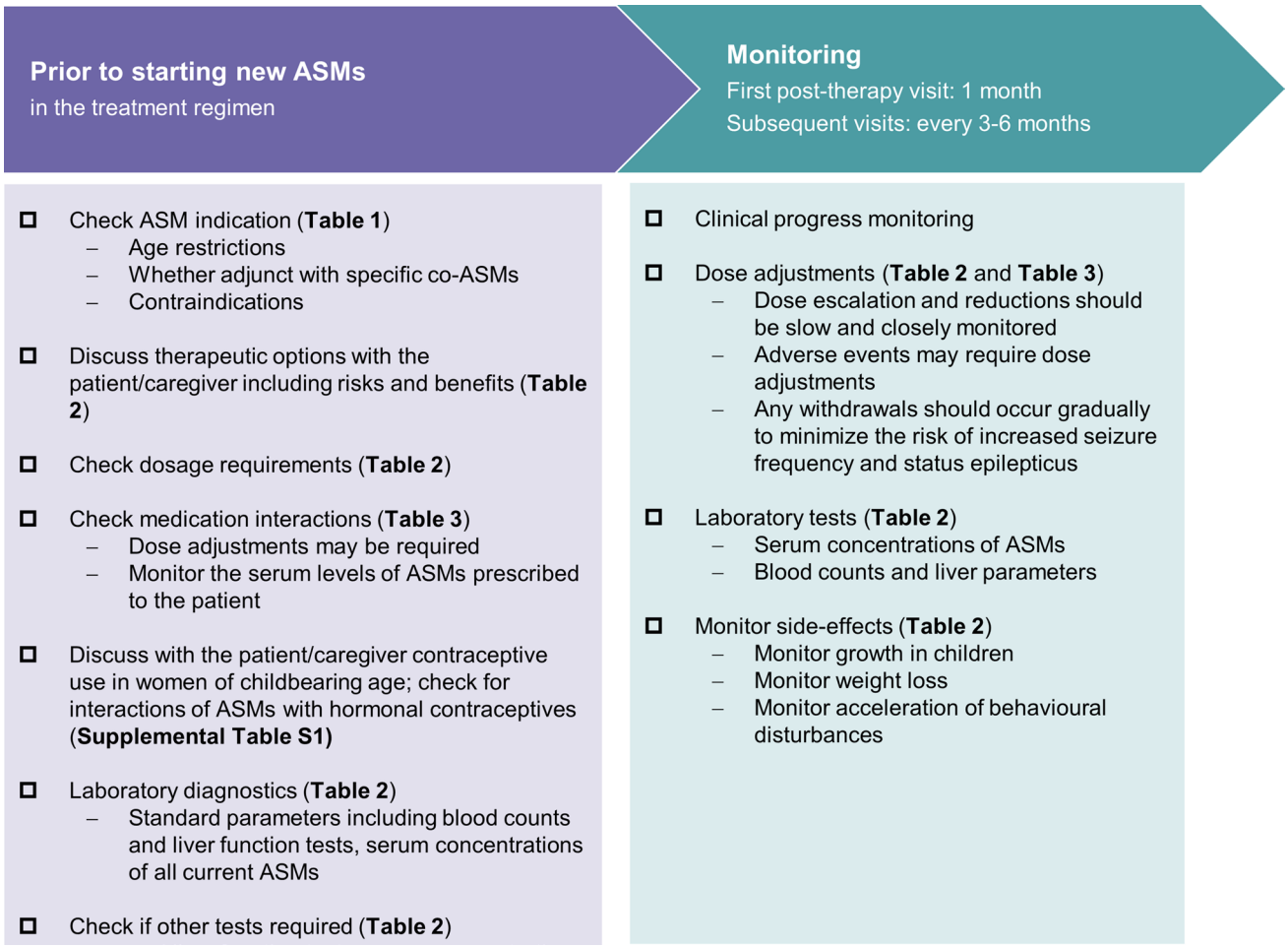


Fig. 3 Checklist to consider through Dravet syndrome treatment. *ASMs* anti-seizure medications

indication as an adjunct treatment for epilepsy [33], while in the USA it is generally used off-label, being only relatively recently approved as an adjunctive treatment of seizures associated with Lennox–Gastaut syndrome (LGS) (Table 1) [34]. Clobazam is a 1,5-benzodiazepine, and as with other benzodiazepines its effects are mediated by binding to the GABA-A receptor, among other mechanisms (Fig. 4). However, CLB has a structure that is different from 1,4-benzodiazepines, with a greater selectivity for α2-GABA-A than α1-GABA-A subunits, which results in fewer sedative effects and a lower propensity for efficacy tolerance (i.e. losing efficacy over time) [35].

Clobazam is administered orally, available in the EU and USA as oral tablets and an oral suspension, while an oral soluble film was approved in the USA in 2018 [36]. The initial dose of CLB is 0.2 mg/kg/day divided into twice daily, followed by gradual increases to reach target doses of 0.3–1 mg/kg/day, up to a maximum of 2 mg/kg/day. Of note, much of the anti-seizure activity of CLB may be mediated through its active metabolite, norclobazam (*N*-desmethyl-clobazam [nCLB]). Because serum concentrations of CLB and nCLB only reach steady state after 5 and 9 days, respectively, dose escalation should not occur more than weekly [33, 34]. There is a high level of intra-individual variability in the plasma concentrations of CLB and nCLB, but monitoring is advisable with regard to specific drug–drug interactions. *N*-desmethyl-clobazam is primarily metabolised by CYP2C19, and patients who are CYP2C19 poor metabolisers (i.e. individuals with variants in *CYP2C19* that lead to reduced or no activity) are recommended to have half the dosage of CLB because of an increased risk of adverse reactions [34].

There is gold-standard evidence from a randomised controlled trial (RCT) related to the efficacy of CLB for LGS [37], and also in conjunction with STP, CBD and FFA in DS (see below), but otherwise the published evidence is limited to two retrospective studies that reported > 50% responder rates of 27.6% and 45.5% in patients with DS treated with adjunct CLB [30, 31]. Clobazam has a fairly benign safety profile: AEs reported in the phase III trial in patients with

Table 1 Eligibility criteria for anti-seizure medications (ASMs)

ASM	Indication EU	Indication USA	Age restriction	Adjunct only	Contraindications
VPA	Generalised, partial or other epilepsy	Monotherapy and adjunctive therapy of complex partial seizures; sole and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures	N	N	Hypersensitivity to the drug or its ingredients Active liver disease Personal or family history of severe hepatic dysfunction Urea cycle disorders Porphyria *POLG* mitochondrial disorders
CLB	Adjunctive therapy in epilepsy	Adjunctive treatment of seizures associated with LGS in patients 2 years of age or older	EU: N USA: ≥2 years in LGS	Y	Hypersensitivity to the drug or its ingredients Severe hepatic insufficiencies (risk of precipitating encephalopathy)
STP	In conjunction with CLB and VPA as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with **DS** whose seizures are not adequately controlled with CLB and VPA	Treatment of seizures associated with **DS** in patients 2 years of age and older taking CLB	EU: N[a] USA: ≥2 years[a]	Y EU: requires CLB+VPA USA: requires CLB	Hypersensitivity to the drug or its ingredients A past history of psychoses in the form of episodes of delirium
CBD (Epidiolex®/ Epidyolex®)[b]	Adjunctive therapy of seizures associated with LGS or **DS**, in conjunction with clobazam, for patients 2 years of age and older; seizures associated with TSC for patients 2 years of age and older	Treatment of seizures associated with LGS, **DS** or TSC in patients 1 year of age and older	EU: ≥2 years USA: ≥1 year	Y EU: requires concomitant CLB USA: no stipulated requirement	Hypersensitivity to the drug or its ingredients Transaminase elevations greater than 3 times the ULN and bilirubin greater than 2 times the ULN
FFA	Treatment of seizures associated with **DS** as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older	Treatment of seizures associated with **DS** in patients 2 years of age and older	≥2 years	Y	Hypersensitivity to the drug or its ingredients Aortic or mitral valvular heart disease Pulmonary arterial hypertension Within 14 days of the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome
TPM	Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with LGS[c]	Adjunctive therapy for adults and paediatric patients (2–16 years of age) with partial-onset seizures or primary generalised tonic-clonic seizures, and for patients ≥2 years of age with seizures associated with LGS[c]	≥2 years	Y[c]	Hypersensitivity to the drug or its ingredients

Table 1 (continued)

ASM	Indication EU	Indication USA	Age restriction	Adjunct only	Contraindications
BR	Germany[d] and Japan: patients with severe epilepsies of infancy and early childhood presenting with generalised tonic-clonic seizures		N	N	Renal failure Known panniculitis or bromoderma under previous bromide therapy Cardiac insufficiency Bronchial asthma Pregnancy

Br bromide, *CBD* cannabidiol, *CLB* clobazam, *DS* Dravet syndrome, *EU* European Union, *FFA* fenfluramine, *LGS* Lennox–Gastaut Syndrome, *STP* stiripentol, *TPM* topiramate, *TSC* tuberous sclerosis complex, *ULN* upper limit of normal, *VPA* valproate

[a]The pivotal clinical studies did not include children below 3 years of age, and therefore it is recommended that children between 6 months and 3 years of age are carefully monitored whilst receiving STP therapy

[b]Epidiolex® (USA)/ Epidyolex® (EU) is the only licenced CBD formulation; it is a highly purified, plant-derived CBD oil-based solution that lacks activity at the cannabinoid receptors and as such does not have euphoric or intrusive side effects

[c]Also indicated for monotherapy for partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures in adults, adolescents and children over 6 years of age (EU) or ≥2 years of age (USA), but is only used as adjunct therapy in patients with DS

[d]Available as a licensed drug in Germany that can be imported to other countries

LGS were consistent with other experiences, and included somnolence, pyrexia, upper respiratory infections, lethargy, drooling and constipation [37, 38]. Clobazam can also be associated with respiratory depression, especially at high doses or with concomitant opioids. No laboratory tests above those recommended for VPA are required (Table 2). Addition of CLB to VPA may increase the plasma concentrations of VPA, and clinical monitoring is recommended with a view to a possible dose adjustment of CLB (Table 3) [33, 34]. Interactions with other relevant ASMs are discussed in the corresponding sections below. Additionally, it is noteworthy that lower doses of drugs metabolised by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be required when used with CLB and lower doses of CLB may be required with strong or moderate CYP2C19 inhibitors (e.g. fluconazole, fluvoxamine, ticlopidine, omeprazole) [33, 34].

4 Stiripentol (STP)

Stiripentol, approved in 2007 in the EU and 2018 in the USA, was the first therapy indicated specifically for the treatment of seizures in patients with DS in conjunction with CLB (with VPA + CLB in the EU). As with other ASMs, STP likely has multiple mechanisms of action connected to its anti-seizure properties that are not fully elucidated [39]. One such mechanism is potentiating GABAergic transmission, acting as a positive allosteric modulator of GABA-A receptors at a site that is different from benzodiazepines; therefore, the combination of STP with a benzodiazepine such as CLB, both acting at different sites, leads to a stronger additive effect compared with either drug alone [40]. In addition, STP increases plasma concentrations of CLB and nCLB via inhibition of CYP enzymes, and these enhanced concentrations may also indirectly contribute to the anti-seizure activity (see below) [41, 42].

Stiripentol is available as hard capsules or a powder for oral suspension. The dose of STP should be escalated gradually, starting with 20 mg/kg/day for 1 week, then 30 mg/kg/day for 1 week, up to a maximum of 50 mg/kg/day in children titrated over an extra 1–4 weeks depending on age (Table 2). Stiripentol has a complex pharmacokinetic profile, requiring consideration of not just weight and drug–drug interactions, but also of age: in older children, adolescents and adults, the dosage is generally lower, in the range of 20–25 mg/kg/day, due to the lower rate of metabolism of adults compared with younger children [43]. The dosage is administered two or three times daily, and because it degrades rapidly in an acidic environment it should be taken with food in order to limit the exposure to gastric acid in an empty stomach [44, 45]. In addition, STP should not be taken with dairy products, carbonated drinks or fruit juice

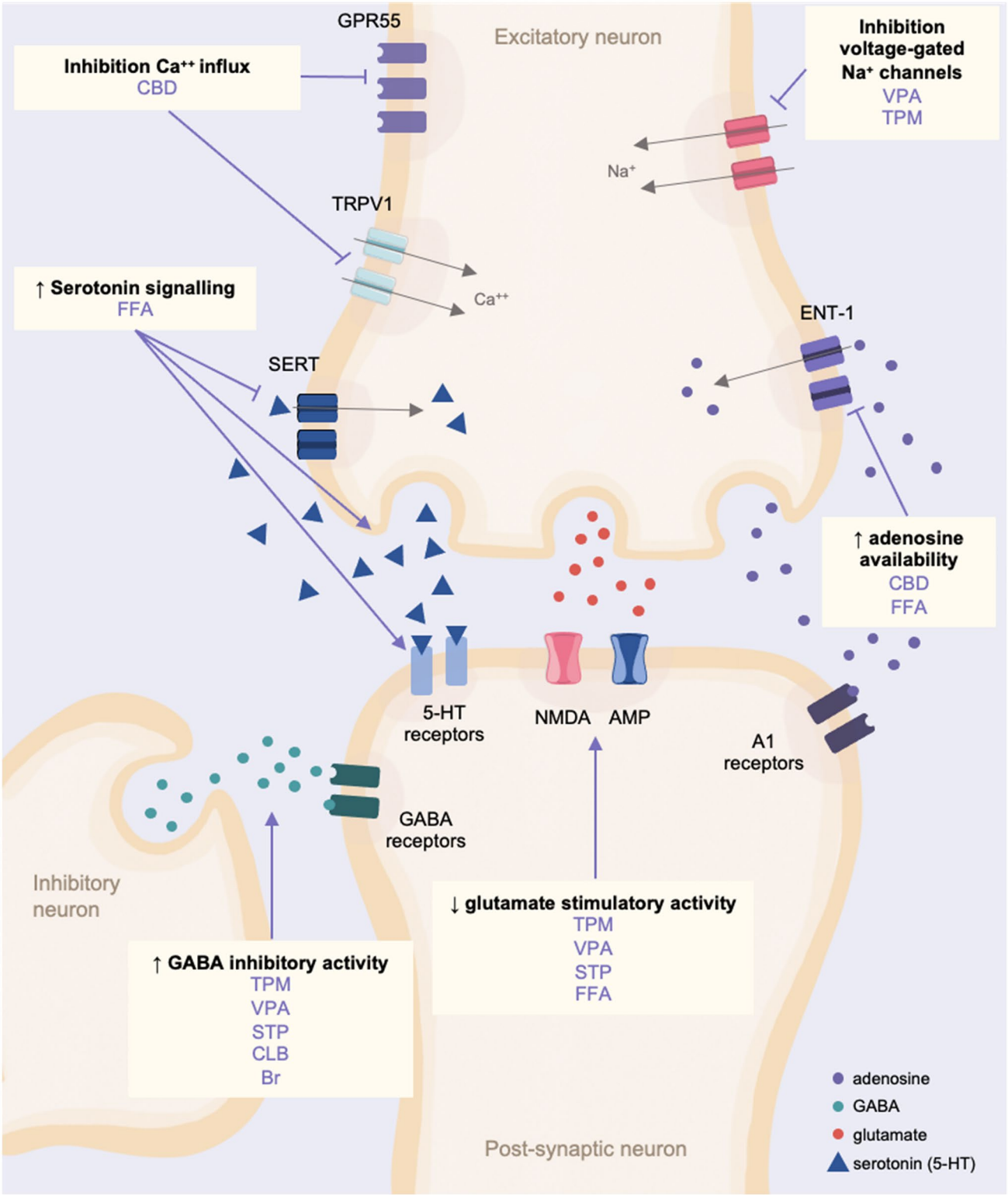


Fig. 4 Simplified schematic of the main known mechanisms of action of the anti-seizure medications used in Dravet syndrome. *Br* bromide, *Ca++* calcium, *CBD* cannabidiol, *CLB* clobazam, *ENT-1* equilibrative nucleoside transporter 1, *FFA* fenfluramine, *GABA* gamma-aminobutyric acid, *GRP55* G protein-coupled receptor 55, *Na+* sodium, *NMDA* N-methyl-D-aspartate, *SERT* serotonin transporter, *STP* stiripentol, *TPM* topiramate, *TRPV1* transient receptor potential vanilloid subtype 1, *VPA* valproate, ↑ increased, ↓ decreased

Table 2 Practical issues for the introduction of anti-seizure medications (ASMs)

ASM	Dosage (mg/kg/day)[a]				Tests		Warnings	Most common AEs	Level of evidence in DS
	Initial	Target	Maximum	Other information	Tests	Timings			
VPA	10–15	25–30	60	Divided into 2× daily for extended-release formulation; or 3× daily otherwise	Liver function Coagulation parameters VPA serum concentrations Ammonia	Baseline 6 weeks 3 months 6 months Yearly intervals Baseline	Hepatotoxicity Foetal risk: pregnancy prevention programme Pancreatitis	Gastrointestinal Headache Somnolence Tremor Asthenia	Weak: Observational studies
CLB	0.2	0.3–1	2	Divided into 2× daily	As for VPA	As for VPA	Concomitant use with opioids resulting in sedation, respiratory depression, coma and death Serious skin reactions, including SJS and TEN Physical and psychological dependence Somnolence or Sedation Efficacy tolerance	Somnolence Pyrexia Upper respiratory infections Lethargy Drooling Constipation	Weak: Observational studies
STP	20	50	3000 mg	Taken with food Divided into 2–3× daily	Growth rate of children Blood count Liver function	Regularly Baseline Every 6 months Baseline Every 6 months	Decreased appetite and decreased weight Neutropenia and thrombocytopenia Somnolence Not recommended for use in patients with impaired hepatic and/or renal function Do not use carbamazepine, phenytoin and phenobarbital in conjunction with STP	Decreased appetite Weight loss Insomnia Somnolence Ataxia, Hypotonia Dystonia Dysarthria Agitation Nausea Tremor	Strong: RCTs Observational studies

Table 2 (continued)

ASM	Dosage (mg/kg/day)[a]				Tests		Warnings	Most common AEs	Level of evidence in DS
	Initial	Target	Maximum	Other information	Tests	Timings			
CBD	5	10	20	Consistently taken either with or without food Divided into 2× daily	Serum transaminases (ALT and AST) and total bilirubin	Baseline[b] 1 month 3 month 6 month Periodically or as clinically required	Hepatocellular injury (transaminase elevations) Somnolence and sedation	Somnolence Decreased appetite Diarrhoea Pyrexia Fatigue Transaminase elevations Insomnia, sleep disorder, poor quality sleep Infections Rash	Strong: RCTs EAP/CUP Observational studies
FFA	FFA: 0.2	FFA: 0.7	FFA: 0.7 or 26 mg/day	Divided into 2× daily	Echocardiogram	Baseline Every 6 months for 2 years Annually thereafter	Valvular heart disease and pulmonary arterial hypertension Decreased appetite and weight Somnolence, sedation and lethargy Serotonin syndrome Glaucoma	Decreased appetite Diarrhoea Pyrexia Fatigue Upper respiratory tract infection Lethargy Somnolence Bronchitis	Strong: RCTs EAP/CUP Observational studies
	FFA+STP: 0.2	FFA+STP: 0.4	FFA+STP: 0.4 or 17 mg/day		Monitor patient weight	Regularly			
TPM	1–2	5–10	400 mg	Divided into 2× daily	Liver and renal function	Baseline	Foetal toxicity Serious skin reactions (SJS and TEN) Acute myopia and secondary angle-closure glaucoma Visual field defects Oligohidrosis and hyperthermia Metabolic acidosis Hypothermia with concomitant VPA Kidney stones[c]	Paraesthesia Anorexia Weight loss Speech disorders Fatigue Dizziness Somnolence Nervousness Psychomotor slowing Abnormal vision Fever	Weak: Observational studies and small, open-label prospective studies
					Ammonia (hyperammonaemia/encephalopathy)	Baseline Symptoms occurring			
					Serum bicarbonate (metabolic acidosis)	Baseline Periodic			

Table 2 (continued)

ASM	Dosage (mg/kg/day)[a]				Tests		Warnings	Most common AEs	Level of evidence in DS
	Initial	Target	Maximum	Other information	Tests	Timings			
BR	10	Children: aged 0.5–3 years: 50–70 Aged 4–15 years: 40–60 Adults: 30–50	80	Generally divided into 2× daily	BR concentrations Renal function and electrolytes	Baseline 3–6 months Baseline	Skin disturbances including bromoderma tuberosum Bromism (chronic toxicity)	Loss of appetite Ataxia Tremor Sedation Tiredness Cognitive slowing, disorientation, stupor Acne Gastritis	Weak: Observational studies Anecdotal (broad acceptance in some countries e.g. Japan, Germany and Israel)

AEs adverse events, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *Br* bromide, *CBD* cannabidiol, *CLB* clobazam, *CUP* compassionate use programme, *DS* Dravet syndrome, *EAP* early access programme, *FFA* fenfluramine, *RCT* randomised controlled trial, *SJS* Stevens–Johnson syndrome, *STP* stiripentol, *TEN* toxic epidermal necrolysis, *TPM* topiramate, *ULN* upper limit of normal, *VPA* valproate

[a]Lower initial dosage may be considered in cases of polypharmacy and up-titration intervals extended in the case of AEs

[b]More frequent monitoring may be required in patients on concomitant VPA or in those with elevated liver enzymes at baseline. Liver transaminases and bilirubin should also be measured within 1 month of changes in the dose of CBD or if there are any changes with medications that are known to impact the liver. CBD should be discontinued in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. In addition, patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes

[c]Avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis or in patients on a ketogenic diet

[44, 45]. Furthermore, food and drinks that contain caffeine or theophylline should be avoided as STP may affect their clearance from the body [44, 45].

The efficacy and safety of STP as an adjunctive treatment with VPA and CLB have been demonstrated in two phase III, double-blind, placebo-controlled RCTs in patients with DS aged ≥ 3 years: STP + VPA + CLB was associated with significantly higher > 50% responder rates compared with placebo+VPA+CLB (71% vs 5% [$p < 0.0001$] in STICLO-France [46, 47] and 67% vs 9% [$p = 0.0094$] in STICLO-Italy) [48]. With a generally good tolerability and safety profile, the main AEs associated with the addition of STP in STICLO-France were drowsiness, hyperexcitability decreased appetite and weight decreased [47]. A further study from the French group in 46 children with DS demonstrated the long-term efficacy of STP + VPA + CLB over a median follow-up of 3 years; the number and duration of seizures significantly decreased, together with the number of convulsive SE events [49]. In addition, patients from this French cohort who initiated treatment with STP + VPA + CLB in childhood continued to see benefits into adulthood over a median duration of 18 years ($n = 40$ patients followed); reductions in seizure (generalised tonic-clonic) frequency and duration continued to be observed, with seizure-free periods of 1–5 years seen in ten patients, while there were no SE events [50]. An open-label trial in Japan ($n = 24$ patients) [51, 52] and a retrospective study in the USA ($n = 82$ children) ([42]) have also provided pivotal evidence of the long-term efficacy and safety of STP. Since then, a post-marketing surveillance study in Japan involving data from 410 patients with DS (aged 0.5–50 years) reported responder rates of 43% for convulsive seizures, 55% for focal impaired awareness seizures, and 62% for generalised myoclonic seizures and/or generalised atypical absence seizures; the main AEs were somnolence (39%) and a loss of appetite (25%) [53]. A number of other observational studies have also confirmed the efficacy and safety of STP in real-world clinical practice across different age groups (including adults [54]) and with various follow-up periods, as recently reviewed [1, 39, 55, 56]. However, studies also suggest that a significant proportion of patients may have inadequate seizure control over the long term, despite the use of this combination of ASMs [57, 58].

Because of the effects of STP on reducing appetite, it is important to monitor the weight of patients and the growth rate of children [44, 45]. In addition, as with other ASMs, STP is associated with neutropenia and thrombocytopenia and therefore complete blood counts should be obtained before initiating treatment and every 6 months thereafter; liver function tests are also recommended [44, 45]. A recent study has also highlighted the increased risk of hyperammonaemic encephalopathy in patients with DS who initiated treatment with STP in adulthood [59]. The increased

Table 3 Drug–drug interactions for anti-seizure medication[a,b,c,d]

	VPA	CLB/nCLB	STP	CBD/7-OH-CBD	FFA/nFFA	TPM	BR
VPA							
Serum levels	-	◆	◆	◆ / ◆	▲ / ▼	▼	◆
Adverse event	-	-	-	-	-	● Encephalopathy &/or hyperammonaemia‡	-
Dose adjustment	-	-	-	-	↓†	-	-
CLB							
Serum levels	▲	-	◆	▲ / ▲	▲ / ▼	◆	◆
Adverse event	-	-	-	-	-	-	-
Dose adjustment	👁	-	-	-	↓†	-	-
STP							
Serum levels	▲	▲ / ▲	-	▲ / ▲	▲ / ▼	◆	◆
Adverse event	-	● Somnolence	-	-	-	-	-
Dose adjustment	-	↓ by 25%	-	-	↓†	-	-
CBD							
Serum levels	◆	◆ / ▲	▲	-	◆	▲	◆
Adverse event	● Transaminase enzyme elevations	● Somnolence & sedation	👁	-	-	👁	-
Dose adjustment	↓	↓	👁	-	-	👁	-
FFA							
Serum levels	◆	◆ / ◆	◆	◆	-	■	▲
Adverse event	-	-	-	-	-	-	👁
Dose adjustment	-	-	-	-	-	-	👁
TPM							
Serum levels	▼	▼	■	▲ / ▲	■	-	◆
Adverse event	● Encephalopathy &/or hyperammonaemia‡	-	-	-	-	-	-
Dose adjustment	-	-	-	-	-	-	-
BR							
Serum levels	◆	◆	◆	◆	◆	◆	-
Adverse event	-	-	-	-	-	-	-
Dose adjustment	-	-	-	-	-	-	-

Adapted from Wheless et al. [21]

Serum concentrations: ▲ the interaction results in an increase of the ASM specified in the column heading; ▼ decrease; ◆ no clinically relevant change; ■ unknown/data not available (relates to the ASM specified in the column heading)

Dose adjustments: ↓ decrease in the dose of the ASM specified in the column heading may be required

Adverse events: ● increased risk of adverse events (relates to the ASM specified in the column heading)

👁 monitoring recommended for AEs and the need for dose adjustments of the ASM specified in the column heading due to potential changes in serum concentrations

7-OH-CBD 7-hydroxycannabidiol, *ASM* anti-seizure medications, *BR* bromide, *CBD* cannabidiol, *CLB* clobazam, *FFA* fenfluramine, *nCLB* N-desmethyl-clobazam, *nFFA* norfenfluramine, *STP* stiripentol, *TPM* topiramate, *VPA* valproate

[a]Because of multiple interactions, it is advisable to monitor the serum concentrations of ASMs prescribed to the patient

[b]FFA dose is restricted to 0.4 mg/kg/day or 17 mg/day when FFA is in combination with STP

[c]Expert opinion from Germany regarding the use of FFA+BR: BR concentrations increased in a proportion of patients after initiation of FFA. Dose reductions of bromide were made in most patients

[d]Encephalopathy or hyperammonaemia in those on VPA/TPM requires discontinuation of either TPM or VPA

ammonia levels occurred despite dose reductions of VPA and CLB, but they were generally normalised with carnitine treatment [59].

Stiripentol increases the plasma concentration of VPA and CLB its active metabolite nCLB. In particular, dose reductions of CLB (of approximately 25% per week) may be required, especially in the event of AEs such as drowsiness, hypotonia and irritability in young children [44, 45]. The interaction with VPA is more moderate, and a dose adjustment of VPA may not be needed, although an increase in gastrointestinal AEs including loss of appetite and loss of weight has been reported, with a suggested dose reduction of VPA of 30% every week [44, 45]. The effects on VPA and CLB are the result of STP being an inhibitor of cytochrome P450, which also has implications for other ASMs and other drugs [44, 45]. Drugs to be generally avoided include immunosuppressants (e.g. tacrolimus, ciclosporin, sirolimus) because of increased blood concentrations of the immunosuppressants, and statins because of the elevated risk of dose-dependent AEs including rhabdomyolysis. Dose reductions may be required with other ASMs including phenobarbital, primidone, phenytoin, carbamazepine, diazepam, ethosuxamide and tiagabine. In addition, concomitant midazolam, triazolam or alprazolam can cause excessive sedation. Furthermore, a dose adjustment may be required with drugs metabolised by CYP2D6 including beta-blockers,

antidepressants (e.g. fluoxetine, paroxetine, sertraline, imipramine, clomipramine), antipsychotics (haloperidol) and analgesics (codeine, dextromethorphan, tramadol).

5 Highly Purified Cannabidiol (CBD)

Highly purified CBD has received approval as an adjunctive therapy for seizures associated with DS, with LGS and most recently, for tuberous sclerosis complex (TSC). It was first approved in the USA in 2018 (Epidiolex®), and in the EU in 2019 (Epidyolex®); in the EU, it is indicated in conjunction with CLB (except for TSC where it is approved without the combination of CLB) (Table 1) [60, 61]. In the USA, it is approved for use in patients aged 1 year and older, while in the EU it is approved for patients aged 2 years and older. As of 2021, Epidiolex/Epidyolex® is the only CBD formulation that has been approved by the US Food and Drug Administration and the European Medicines Agency (referred to as CBD throughout). It is a highly purified, plant-derived, CBD oil-based solution that does not contain tetrahydrocannabinol, and as such does not have euphoric or intrusive side effects. Cannabidiol has mechanisms of action that are distinct from other ASMs (Fig. 4): it modulates intracellular calcium via both G-protein-coupled receptor 55 and transient receptor potential vanilloid 1, and also inhibits adenosine cellular uptake via the equilibrative nucleoside transporter 1 [62].

Cannabidiol is available as an oral solution at 100 mg/mL. It is given twice a day, with a recommended starting dose of 5 mg/kg/day for 1 week, followed by an increase to a maintenance dose of 10 mg/kg/day. Thereafter, it can be gradually titrated by 5 mg/kg/day up to a maximum of 20 mg/kg/day depending on clinical response and tolerability. It has been noted that slow titration of CBD, i.e. reaching a target dose of 10 mg/kg/day within at least 1 month and then gradually increasing to a maximum dose of 20 mg/kg/day, results in better tolerance with equivalent efficacy [63]. As food may increase the concentrations of CBD, it should consistently be taken either with or without food, with a preference for taking it with food at approximately the same time each day [64].

The efficacy and safety of CBD in DS was evaluated in two phase III, double-blind, placebo controlled RCTs (GWPCARE1 [CBD 20 mg/kg/day] and GWPCARE2 [CBD 10 and 20 mg/kg/day]) [65, 66]. In a highly refractory population (a median of four prior ASMs and three concomitant ASMs), responder rates were significantly higher compared with placebo (42.6–49.3% vs 26.2–27.1%), and were even higher in a subgroup of patients taking concomitant CLB (47.5–62.5% vs 23.7–36.6%). Because of this potential enhanced efficacy with CLB, the approval from the European Medicines Agency stipulates that CBD be used in conjunction with CLB. Cannabidiol was also associated with improvements in overall condition assessed using the Caregiver Global Impression of Change, as well as increases in seizure-free days. Longer term efficacy and safety (up to 3 years) has been determined in an open-label extension of the pivotal phase III trials [67, 68], and importantly from an expanded access programme confirming its efficacy in real-world clinical practice [69–72].

Cannabidiol has been generally well tolerated across studies in patients with DS and LGS; the most common AEs from a pooled analysis were somnolence (particularly with concomitant CLB, see below), decreased appetite, diarrhoea, fatigue, malaise, asthenia, rash, insomnia and infections [60, 61]. Of note, a low-fibre diet may be considered during up-titration if the patient experiences diarrhoea.

Bi-directional interactions occur with CLB producing an increase in plasma concentrations of 7-OH-CBD (the major metabolite of CBD) and of nCLB by three-fold, a reason behind its enhanced efficacy compared with CBD without CLB, although it should be noted that CBD without CLB is also efficacious (Table 3) [73–75]. However, the interaction may also lead to an increase in AEs, particularly somnolence and sedation, requiring a dose reduction of CLB. In addition, CBD is associated with elevations of liver transaminases particularly in patients taking concomitant VPA; patients taking higher doses of CBD, and to a lesser extent concomitant CLB also had an increased incidence of transaminase elevations [60, 61]. Because of a risk of liver injury, serum transaminases (alanine aminotransferase and aspartate transaminase) and total bilirubin levels should be obtained prior to initiating CBD, after 1 month, 3 months and 6 months and then periodically or as clinically required (Table 2) [60, 61]. More frequent monitoring may be required in patients taking concomitant VPA or in those with elevated liver enzymes at baseline. Cases of thrombocytopenia have also been observed in some patients taking concomitant CBD and VPA [76]. With regard to other drug–drug interactions, a dose increase of CBD may be required if co-administered with medications that are strong inducers of CYP3A4 (e.g. enzalutamide, phenytoin) or CYP2C19 (e.g. rifampin, carbamazepine, phenobarbital, phenytoin, St. John's wort) [60, 61, 77].

6 Fenfluramine (FFA)

Fenfluramine as an add-on therapy was approved for the treatment of seizures associated with DS in mid-2020 in the USA and in late 2020 in the EU [78, 79]. Fenfluramine is a repurposed drug, having originally been used in adults at high doses (up to 120 mg/day) in combination with phentermine (fen-phen) as a therapy for obesity until 1997 when it was withdrawn because of increased cases of cardiac valve

disease, although it should be noted that phentermine also has an impact on valvular disease [80]. However, because of its role in stimulating the central serotoninergic pathways, as well as a few early case reports indicating its efficacy in patients with seizure disorders, FFA continued to be investigated as an ASM, with studies proceeding in Belgium where a Royal Decree was issued to allow FFA to be used at low doses in children with intractable epilepsy [80]. These studies, with favourable results in patients with DS [81, 82], were instrumental in paving the way for further clinical development that ultimately led to regulatory approval in patients with DS.

Fenfluramine is available as a 2.2-mg/mL oral solution. It is taken twice daily, with different dosing schedules according to whether the patient is taking STP because of an interaction whereby STP increases plasma concentrations of FFA and decreases its metabolite, norfenfluramine (Table 3) [83]. In both instances (i.e. with or without STP), an initial dose of 0.2 mg/kg/day is recommended, increased to 0.4 mg/kg/day after 7 days; 0.4 mg/kg/day is the recommended maintenance dose in patients taking STP, whereas in patients not taking STP, a further increase to the suggested maintenance dose of 0.7 mg/kg/day can occur after another 7 days [78]. Patients should not exceed the maximum daily dose of 17 mg when taking STP or 26 mg when not taking STP.

Fenfluramine has a unique mechanism of action compared with other ASMs. Fenfluramine targets the serotonergic system, in multiple ways including promoting serotonin (5-HT) release into the synapse, inhibiting the serotonin transporter, and acting as an agonist at multiple 5-HT receptors [84]. In addition, FFA was found to be a positive modulator of the sigma-1 receptor, a molecular chaperone that has roles in neuronal signalling; studies in a mouse model suggested that this mechanism of action could have implications for improved cognitive functions of spatial and contextual learning [85].

The efficacy and safety of FFA have been evaluated in three pivotal, phase III, double-blind, placebo-controlled RCTs in patients aged 2–18 years with DS; two trials conducted in patients without STP were identical and the results were merged [86], while the other trial exclusively included patients taking STP [87]. In patients who were highly drug resistant (baseline convulsive seizure frequencies of 14–20 per month despite the majority taking three or more concomitant ASMs), ≥ 50% responder rates for convulsive seizures were significantly higher compared with placebo (68–38% vs 5–12%). Fenfluramine was also associated with significantly longer seizure-free intervals, a significantly higher number of convulsive seizure-free days and improvements in achieving near-seizure freedom (< 1 seizure over the 14-week treatment period) [86–88]. In addition, compared with placebo, more patients were rated as "very much" or "much improved" according to the Clinical Global Impression-Improvement. Data from an open-label extension trial have shown that reductions in convulsive seizure frequency are sustained over a median duration of treatment of 3 years [89]. Furthermore, real-world data obtained via a compassionate use programme have shown that FFA had a good retention rate, and as well as reductions in seizures and seizure days per months, FFA was associated with reductions in episodes of SE and reductions in the number of concomitant ASMs [90, 91]. Moreover, case reports have described the use of FFA for the successful treatment of nonconvulsive SE in an 8-year-old patient [92] and super-refractory SE in a child [93] and a 20-year-old adult [94]. Additionally, FFA may be associated with reductions in all-cause and sudden unexpected death in epilepsy mortality rates in patients with DS [95].

Fenfluramine is generally well tolerated. In-line with the anorexigenic effects of FFA that were harnessed when it was used as an anti-obesity therapy, decreased appetite and weight loss are among the most common AEs [78, 79]. Decreased weight is dose dependent, and an additive effect has been observed when FFA is combined with other ASMs such as STP or TPM. However, most patients resume weight gain over time while continuing treatment. Other common AEs include diarrhoea, fatigue, lethargy, pyrexia and upper respiratory tract infection.

Importantly, no signs of heart valve disease have been documented to date [96]. However, echocardiogram monitoring should be conducted before initiating FFA and then every 6 months for the first 2 years, with annual echocardiograms thereafter [78, 79]. In addition, FFA is contraindicated in patients with aortic or mitral valvular heart disease and pulmonary arterial hypertension. In the EU, clinicians will need to register with a controlled access programme before initiating FFA for the first time [79]. The controlled access programme is a requirement of the European Medicines Agency to ensure that clinicians do not use FFA off-label in weight management in obese patients and to confirm the need for periodic cardiac monitoring. Similarly, in the USA, clinicians, pharmacies and patients need to enrol in the REMS (Risk Evaluation and Mitigation Strategy) programme, which provides education about the risks of valvular heart disease and pulmonary arterial hypertension and the need for monitoring [78]. Other warnings include serotonin syndrome, a potentially fatal condition caused by excessive accumulation of serotonin in the body, which can occur particularly if co-administered with other serotonergic drugs (Table 2) [78, 79]. No particular requirements for dose adjustments of the ASMs of relevance for DS have been documented (Table 3), except for observations that bromide concentrations may be increased in some patients treated with FFA + bromide (expert opinion). Of note, data from the compassionate use programme in Europe suggest that FFA use can ultimately lead to reductions in the ASM drug

load, associated with reductions in concomitant ASM use or in dose reductions [90, 91]. Finally, an increase in FFA dosage is recommended when co-administered with rifampin or a strong CYP1A2 and CYP2B6 inducer. Similar to CBD combinations with VPA, FFA may exacerbate VPA-induced thrombocytopenia [97].

7 Topiramate (TPM)

Topiramate, an ASM with a broad range of antiseizure activity, is indicated as adjunctive therapy in persons aged 2 years and above with partial-onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with LGS [98, 99]. Its mechanisms of action relating to seizure control are complex and not fully elucidated, but they may include blocking voltage-dependent sodium channels, enhancing the GABAergic pathway, antagonizing the glutamate receptor (the AMPA/kainate subtype), and inhibiting the carbonic anhydrase enzymes II and IV (Fig. 4) [100, 101].

Topiramate is available as capsules, film-coated tablets, an oral solution and sprinkle capsules; the latter can be given with (sprinkled over) a small amount of soft food. Topiramate is administered twice daily starting at 1–2 mg/kg/day, with doses gradually increased to a target dosage of 5–10 mg/kg/day depending on tolerance and efficacy. Slow titration is important to reduce AEs.

Evidence of efficacy in patients with DS is derived from two small, prospective, open-label studies and a handful of small retrospective observational studies that have reported > 50% responder rates of between 35% and 78% [14, 102]. Larger RCTs have been conducted in patients with LGS and in patients with partial-onset or primary generalised tonic-clonic seizures [98, 99, 103].

Topiramate has a generally acceptable tolerability and safety profile. A pooled analysis of TPM as an adjunct therapy across the epilepsy/LGS trials showed that the most common AEs were somnolence, fatigue, nausea, dizziness, ataxia, anorexia, paresthesia, anorexia, weight loss, and various cognitive/neuropsychiatric problems including nervousness, psychomotor slowing, difficulty with memory, speech disorders/related speech problems and personality disorder (behavioural problems) [98, 99]. Tolerability may be improved by slow titration with 2-week intervals [104]. Topiramate is also associated with a number of warnings requiring monitoring including visual defects, oligohidrosis and hyperthermia, metabolic acidosis, hyperammonaemia/encephalopathy (especially with concomitant VPA) and kidney stones (Table 2) [98, 99]. Regarding the latter, staying hydrated by drinking plenty of fluids minimises the risk of kidney stones. The addition of TPM does not need any particular adaptation of dosages for the other ASMs used in DS (Table 3) [98, 99]. Decreased efficacy of oestrogen-containing contraceptives has been reported with high doses of TPM (≥ 200 mg), and in those situations non-hormonal forms of contraception are recommended (Table S1 of the ESM).

8 Bromide

Bromide is one of the oldest ASMs dating back to 1857; it lost favour for the treatment of seizures after the discovery of phenobarbital in 1912, but had a resurgence in some countries following reports in the 1980s and 1990s of efficacy in refractory epileptic syndromes. Bromide is not available in many countries; however, in Germany and Japan, it is approved for patients with severe epilepsies of infancy and early childhood presenting with generalised tonic-clonic seizures, including DS [105]. Its mechanisms of action are not fully understood; however, it may increase GABA-ergic inhibition [105].

The target dosage of bromide is between 30 and 70 mg/kg/day [depending on age (Table 2)], given orally generally in two equal doses. It is available predominantly as potassium bromide tablets. The evidence base related to the efficacy of bromide in DS comes from a number of retrospective studies, which have reported > 50% responder rates of between 28% and 78% [30–32, 106, 107], together with its common use in some countries, thus inferring good efficacy [15].

Bromide is generally well tolerated at the low doses currently prescribed in children with refractory epilepsy. Adverse events can typically include loss of appetite, weight loss, ataxia, tremor, sedation, tiredness, cognitive slowing, disorientation, stupor, respiratory tract infections, gastritis and gastric ulcers. The risk of developing gastric ulcers can be reduced by using gastric acid-resistant capsules that can be prepared by the pharmacist using the tablets or potassium bromide salt. In addition, skin disturbances can occur, which may require the dosage to be reduced if troublesome, including rash, acne, ulcerations and bromoderma tuberosum (vegetating inflammation). The latter is rare but can be serious leading to scars, and because it does not appear to be dose dependent, it requires cessation of bromide treatment.

Bromide does not undergo hepatic metabolism and it is not subject to the same number of drug–drug interactions as other ASMs [105, 108]. However, a drug–food interaction can occur with the chloride ion, especially with table salt (sodium chloride), and as such it is recommended that a consistent and limited amount of sodium chloride be ingested. It is also important that prior to initiating bromide, renal function and electrolyte disturbances should be assessed and regular examinations are required to determine serum bromide

concentrations. Furthermore, electrolyte imbalances during treatment (e.g. due to fluid loss because of severe vomiting, diarrhoea or excessive sweating) can also lead to increased AEs, requiring careful monitoring. In the case of an infection, children might require only half of their prescribed dose to prevent side effects caused by the accumulation of bromide in the body. Clinicians should also be aware that chloride levels may be falsely elevated in blood tests due to cross-reactivity with bromide during the testing procedure.

9 Other Anti-Seizure Medications (ASMs) and Clinical Trials

Other ASMs that could be considered include levetiracetam, brivaracetam, perampanel, zonisamide and ethosuximide; however, it should be noted that there is little evidence of their efficacy for controlling seizures in DS. Of note, ethosuximide is generally the preferred treatment for patients with absence seizures, with studies finding it more effective and/or more tolerable than VPA and lamotrigine in children with newly diagnosed childhood absence epilepsy [109, 110]. Furthermore, studies reporting on prescription patterns show that levetiracetam is frequently discontinued in patients with DS over time [111], suggesting a lack of long-term efficacy and/or tolerability, while caregivers of patients with DS scored it as only "somewhat effective" [112]. Practical details of these ASMs are provided in Table S2 of the ESM. Of particular importance in DS is that some ASMs tend to exacerbate seizures in patients with DS and should generally be avoided; these include sodium channel blockers such as carbamazepine, eslicarbazepine acetate, lacosamide and lamotrigine, oxcarbazepine and phenytoin, and ASMs acting on GABA, such as tiagabine, vigabatrin, gabapentin and pregabalin (Fig. 2).

Enrolling patients in clinical trials is also a consideration. Of the investigational agents, soticlestat (OV935/TAK-935), a first-in-class suppressor of cholesterol 24-hydroxylase (CH24H), is furthest along in clinical development, with a phase III study planned in patients with DS and LGS following positive results from the phase II ELEKTRA trial (NCT03650452) and the ENDYMION trial [113]. Furthermore, technological advances in developing genetic therapies are being harnessed for the treatment of DS, including antisense oligonucleotides, CRISPR/Cas9-mediated genome editing, and gene regulation therapy that uses an adeno-associated virus vector containing a transcription factor to increase protein production [114]. Genetic therapies for DS aim to restore the expression of $Na_V1.1$, and by addressing the underlying aetiology/pathophysiology they have the potential to dramatically slow or even stop disease progression across all or many aspects of the syndrome (i.e. the different types of seizures and cognitive dysfunction). Of note, STK-001, an ASO designed to upregulate $Na_v1.1$ from the functioning wild-type allele, has entered phase I/II clinical development, with other genetic therapies not far behind.

10 Conclusions

While we have provided an overview of the practical issues surrounding the use of ASMs for the treatment of seizures in patients with DS, there remain several unanswered questions for clinicians that require further evidence. First, there are currently no head-to-head trials of CBD vs FFA, and therefore the decision as to which option to choose is mainly based on clinicians' experience, individual patient factors and patient/caregiver preferences, as well as availability within individual countries. The latter is important to point out—not all treatments described here are available in all countries. Additionally, it is noteworthy that it is currently difficult to choose an ASM based on the seizure type, although ethosuximide is better suited for absence seizures. Second, evidence around improvements in cognitive dysfunction and in quality of life is still generally lacking, although there are the beginnings of evidence that FFA and CBD have the potential for improvements in these highly relevant treatment goals [115–117]. In addition, while it is known that the burden of illness and healthcare costs of DS are high [118–123], there is a lack of published evaluations regarding the cost effectiveness of the ASMs used to treat patients with DS. Furthermore, in clinical practice, ASMs may be given off-label to patients who are younger than the indicated age, and there is a lack of information about the dose, safety and tolerability in these cases. Finally, while the approval of STP, CBD and FFA undoubtedly represent tremendous progress, DS still poses a heavy burden for patients and their families. To make further progress, a number of challenges still need to be overcome including improving early diagnosis to allow for prompt and appropriate treatment, reductions in polypharmacy, improvements in quality of life, the availability of additional treatments for those who do not benefit on those currently available and the identification of biomarkers to aid the tailoring of treatments to the individual patient.

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